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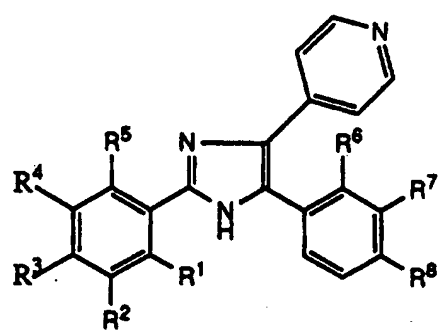
(54) Title: IMIDAZOLE DERIVATIVES AS PROTEIN KINASE INHIBITORS IN PARTICULAR EGF-R TYROSINE KINASE

(57) Abstract

Imidazole derivatives of general formula (I), wherein R^1-R^8 each independently signify hydrogen, lower-alkyl, substituted lower alkyl, lower-alkenyl, lower-alkoxy, substituted lower alkoxy, lower-alkoxycarbonyl, halogen, hydroxy, amino, mono- or di(lower-alkyl)amino or nitro, and pharmaceutically usable salts thereof are protein kinase inhibitors and can be used as medicaments, e.g. for the control of hyperproliferative disorders such as atherosclerosis, psoriasis and tumors as well as of alopecia.



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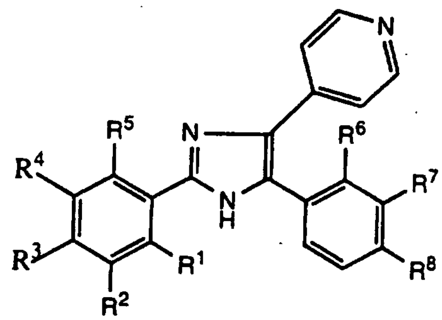
Imidazole derivatives as protein kinase inhibitors in particular EGF-R tyrosine kinase

The invention is concerned with novel imidazole derivatives of the general formula



(I)

wherein R^1-R^8 each independently signify hydrogen, lower-alkyl, substituted lower alkyl, lower-alkenyl, lower-alkoxy, substituted lower alkoxy, lower-alkoxycarbonyl, halogen, hydroxy, amino, mono- or di-(lower-alkyl)amino or nitro, and pharmaceutically usable salts thereof.

The term "lower-alkyl" used here, alone or in combination, signifies a straight-chain or branched alkyl group with 1-6 C atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.-butyl, isobutyl, tert. butyl, n-pentyl and n-hexyl. The terms "substituted lower alkyl" and "substituted lower alkoxy" signify lower-alkyl and, respectively, lower-alkoxy groups which are substituted, for example, by lower-alkoxy, lower-acyloxy, azido, cyano, amino, di(lower-alkyl)amino, heterocyclyl, hydroxy or halogen. The term "halogen" or "halo" embraces fluorine, chlorine, bromine and iodine. Heterocyclyl signifies a 5- or 6-membered saturated N-heterocycle which optionally contains a further nitrogen atom or an oxygen atom, e.g. morpholino, piperazino, piperidino or pyrrolidino and which can be substituted by lower-alkyl, substituted lower alkyl or lower-alkoxycarbonyl, such as 2,6-dimethylmorpholino, N_4-substituted piperazino, C_4-substituted piperidino or C_2-substituted pyrrolidino.

Preferred compounds of formula I are those in which R^1 signifies lower-alkyl, lower-haloalkyl or halogen, especially lower-alkyl or halogen, R^2 signifies hydrogen, lower-alkyl, substituted lower alkyl, lower-alkoxy, substituted lower alkoxy, lower-alkoxycarbonyl, halogen, hydroxy, amino or nitro, especially hydrogen, hydroxy, nitro, lower-alkoxycarbonyl, di-(lower-alkyl)amino-lower-alkyl, morpholino-lower-alkyl or 4-methylpiperazinyl-lower-alkyl, R^3 signifies hydrogen, lower-alkyl, substituted lower-alkoxy or hydroxy, especially hydrogen or lower-alkyl, R^4 signifies hydrogen, lower-alkyl or nitro, especially hydrogen, R^5 signifies lower-alkyl, lower alkoxyalkyl, lower-haloalkyl, allyl, amino, di(lower-alkyl)amino, halogen or nitro, especially amino or lower-alkyl, R^6 signifies hydrogen, substituted alkyl or halogen, especially hydrogen, R^7 signifies hydrogen, lower-alkyl, lower-alkoxy, hydroxy or halogen, especially hydrogen or lower-alkyl, and R^8 signifies hydrogen or halogen. Methyl and isopropyl are preferred lower-alkyl groups. Chlorine is a preferred halogen.

Examples of preferred compounds of formula I are:

4-[5-(4-Chlorophenyl)-2-(2,4,6-trimethylphenyl)imidazol-4-yl]pyridine,

4-[5-(3-methylphenyl)-2-(2,4,6-trimethylphenyl)imidazol-4-yl]pyridine,

3-chloro-2-[4-(4-chlorophenyl)-5-pyridin-4-yl-imidazol-2-yl]phenylamine,

4-[5-(4-chlorophenyl)-2-(2,6-diisopropylphenyl)imidazol-4-yl]pyridine,

methyl 3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzoate,

4-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]morpholine,

[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]dimethylamine,

1-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]-4-methylpiperazine,

4-[5-(4-chlorophenyl)-2-(2,4,6-trimethyl-3-nitrophenyl)-

imidazol-4-yl]pyridine and

3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylphenol.

The compounds of formula I which contain acidic functions can form pharmaceutically usable salts with bases such as alkali metal hydroxides (e.g. sodium hydroxide and potassium hydroxide), alkaline earth metal hydroxides (e.g. calcium hydroxide and magnesium hydroxide) and ammonium hydroxide and the like. The compounds of formula I which contain basic functions can form pharmaceutically usable salts with acids. As such salts there come into consideration not only salts with inorganic acids such as hydrochloric acid or hydrobromic acid, sulphuric acid, nitric acid and phosphoric acid, but also salts with organic acids such as acetic acid, tartaric acid, succinic acid, fumaric acid, maleic acid, malic acid, salicylic acid, citric acid, methanesulphonic acid, p-toluenesulphonic acid etc.

The present invention is accordingly concerned with compounds of formula I and their pharmaceutically usable salts per se and for use as therapeutically active substances, a process for the manufacture of these compounds and their salts, medicaments which contain these compounds or salts and the production of these medicaments and the use of the compounds and their salts for the control of illnesses, especially hyperproliferative disorders such as atherosclerosis, psoriasis and tumours and for the treatment of alopecia, or for the production of a medicament for the treatment and prevention of such disorders.

The pharmacological activity of the compounds in accordance with the invention can be determined on the basis of their activity as protein kinase inhibitors and inhibitors of HaCaT-cell proliferation. In particular, the compounds in accordance with the invention are selective inhibitors of epidermal growth factor receptor (EGF-R) tyrosine kinase.

EGF-R plays a rôle in the development and metastation of certain human malignant diseases such as breast cancer, cancer of the liver and cancer of the prostate.

For all known functions and activities of EGF-R its tyrosine kinase activity is a determining factor. The inhibition of this enzymatic activity by the compound of formula I can therefore be looked upon as a measurement for the efficacy in the therapeutic treatment of EGF-R-mediated hyperproliferative diseases such as certain forms of cancer and psoriasis.

In contrast to the stimulating rôle of the EGF receptor in keratinoycyte proliferation, in vitro and in vivo studies show that the activation of this receptor is a negative regulator of hair follicle activity. Thus, the injection of EGF inhibits hair growth in newborn mice (Moore et al., J. Endocrinol <u>88</u>, 293 [1981]) and sheep (Chapman & Hardy from J. Biol. Sci. <u>41</u>, 261 [1988]) and the treatment of cultured human hair follicles with EGF induces a catagen-like state (Philpott et al., J. Cell Sci. <u>97</u>, 463 [1990]) with inhibition of hair fibre production. These findings suggest that inhibition of EGF-R tyrosine kinase stimulates hair growth and lengthens the duration of the anagen phase of the hair cycle in vivo.

The biological activity of the compounds in accordance with the invention was tested in various test models which are described hereinafter.

<u>Tyrosine protein kinases</u>

<u>Inhibition of EGF-receptor tyrosine kinase</u>

The activity of EGF-receptor tyrosine kinase is determined by measuring the transfer of ^{32}P-labelled phosphate from ^{32}P-γ-ATP (10 μM) to the substrate RR-scr peptide* (0.75 mM). A membrane fraction from human A431 cells is used as the enzyme. It is isolated according to Thom et al., Biochem. J. <u>168</u>, 187 (1977) and stored at -75°C (4-6 mg protein/ml). The compounds are

tested in 10% DMSO in a concentration of 0.001-100 μM. The incubation is carried out at 30°C for a period of 30 minutes in Tris buffer (25 mM, pH 7.4) which contains magnesium acetate (30 mM), sodium vanadate (0.5 mM), 0.5% BSA and 0.05% Triton X-100. The membranes are pre-incubated with 2 μM of EGF at 4°C for 90 minutes. The test is started by adding the enzyme (2 μg of membrane protein) and terminated by adding ice-cold KH_2PO_4 (1M, pH 3.0). After centrifugation the labelled peptide is separated from excess ATP in the supernatant by reversed phase HPLC. The peptide fraction is collected and the radioactivity is measured in a standard β-counter or on-line with a radiometer (Berthold). The inibitory activity of the test compound is expressed as the mikromolar concentration which is required for 50% inhibition (IC_{50} [μM]).

*RR-src peptide = [Arg-Arg-Leu-Ile-Glu-Asp-Ala-Glu-Tyr-Ala-Ala-Arg-Gly]

Inhibition of $p56^{lck}$ tyrosine kinase

The activity of $p56^{lck}$ tyrosine kinase is determined by measuring the transfer of ^{32}P-labelled phosphate from ^{32}P-γ-ATP (10 μM) to the substrate RR-src peptide* (0.75 mM). Human recombinant $p56^{lck}$ (expressed in E. coli) is used as the enzyme. It is purified from the soluble fraction by means of a monoclonal antibody column and stored at -75°C. The compounds are tested in 10% DMSO in a concentration of 0.001-100 μM. The incubation is carried out at 30°C for a period of 30 minutes in HEPES buffer (50 mM, pH 6.9) which contains manganese chloride (11 mM) and 0.5% BSA. The test is started by adding the enzyme and terminated by adding ice-cold KH_2PO_4 (1M, pH 3.0). After centrifugation the radiolabelled peptide is separated from excess ATP in the supernatant by reversed phase HPLC. The peptide fraction is collected and the radioactivity is determined in a standard β-counter or on-line with a radiometer (Berthold). The inhibitory activity of the test compound is expressed as the micromolar concentration which is required for 50% inhibition (IC_{50} [μM]).

Serine/threonine protein kinases

Inhibition of cAMP-dependent protein kinase (PKA)

The activity of PKA is measured by measuring the transfer of ^{32}P-labelled phosphate from ^{32}P-γ-ATP (10 μM) to the substrate histone H1 (333 μg/ml) using partially purified PKA from hog brain (DEAE chromatography according to U. Kikkawa et al., Methods Enzymol. 99, 288, 1983). PKA is activated by 2 μM of cAMP in Tris HCl buffer (20 mM, pH 7.4). The compounds are tested in DMSO/buffer at a concentration of 0.001-100 μM. The test is started by adding the enzyme, takes 2 minutes at 32°C and is terminated by adding 20% trichloroacetic acid (containing 1% SDS and 1% sodium pyrophosphate). The precipitated protein, which contains the radiolabelled histone, is separated from excess ATP by filtration through a nitrocellulose membrane filter. The radioactivity on the filter is determined in a scintillation counter. The inhibitory activity of the test compounds is expressed as the micromolar concentration which is required for 50% inhibition (IC_{50} [μM]).

Inhibition of protein kinase C (PKC)

The activity of PKC is measured by measuring the transfer of ^{32}P-labelled phosphate from ^{32}P-γ-ATP (10 μM) to the substrate histone H1 (200 μg/ml) using partially purified PKC from hog brain (DEAE chromatography according to U. Kikkawa et al., Methods Enzymol. 99, 288, 1983). PKC is activated by phospholipid vesicle prepared by sonicating a mixture of 0.05 ml of phosphatidylserine (10 mg/ml) and 0.005 ml of diolein (10 mg/ml) in 5 ml of Tris HCl buffer (20 mM, pH 7.4). The compounds are tested in DMSO/buffer at a concentration of 0.001-100 μM. The test is started by adding the enzyme, takes 2 minutes at 32°C and is terminated by adding 20% trichloroacetic acid (containing 1% SDS and 1% sodium pyrophosphate). The precipitated protein with the labelled histone is separated from excess ATP by filtration over a nitrocellulose membrane filter. The radioactivity on the filter is measured in a scintill-

ation counter. The inhibitory activity of the test compound is expressed as the micromolar concentration which is required for 50% inhibition (IC_{50} [μM]).

Inhibition of HaCaT cell proliferation

HaCaT is a spontaneous immortalized human keratinoycte cell line (Boukamp et al. 1988) which has been used many times as a model system for hyperproliferative keratinoyctes. The incorporation of [^{3}H]-thymidine was used to quantify the growing cells in the S phase of the cell cycle. The cells were cultivated with a 3:1 mixture of DMEM/F12 medium which had been supplemented with 5% FCS, EGF (10 μg/l), hydrocortisone (400 μg/l), cholera toxin (8.5 μg/l), insulin (5 μg/l), L-glutamine (2 mM) and penicillin/streptomycin. 200 μl of medium were placed in microtitre plates such that each sample contained 5000 cells. The test compounds were added in serial dilutions in the range of 1×10^{-8} M to 1×10^{-5} M at the beginning of the cultivation. The cells were incubated at 37°C for 48 hours. For the last 6 hours [^{3}H]-thymidine was added (1 mCi/sample). After digesting the cells with trypsin the amount of incorporated radioactivity was quantified with a liquid scintillation counter.

The inhibition of selected protein kinases in vitro and the inhibition of cell proliferation in HaCaT-cells by these compounds are set forth in the following Table.

Example	IC_{50} (µM)				
	Isolated enzyme				Cells
	EGF-R	$p56^{lck}$	PCK	PKA	HaCaT
1	0.34	2.2	>100	6.3	2
13	0.80	6.0	>100	190	2
58	0.31	2.2	n.t	n.t	0.8
27	0.13	3.1	100	0.47	3.5
34	0.14	3.8	80	6.0	0.23
38	0.26	5.1	>100	43	0.1
40	0.05	1.65	7.0	5.0	0.57
45	0.05	1.8	37	1.5	0.1
54	0.78	4.95	n.t.	n.t.	0.67
66	0.29	14	23	1.8	2

n.t.: not tested

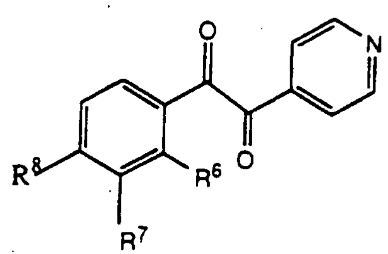
Stimulation of cell proliferation in cultured mouse hair follicles

Mouse hair follicles are isolated and cultured according to the method described by Buhl et al., J. Invest. Dermatol. 92, 315 (1989). Whisker parts are removed from CD-1 mice aged 4 days and the hair follicles are carefully separated from surrounding tissue under the microscope. Hair follicles are cultured in M199 medium which contains 20% FBS and the cell proliferation is

determined from the incorporation of [^{3}H]-thymidine in DNA. The test compounds are dissolved in DMSO and added in serial dilutions in the range of 1 x 10^{-8} to 1 x 10^{-6} M at the beginning of the cultivation. After 1 day 5 µCi/ml of [^{3}H]-thymidine are added to the culture medium and the follicles are incubated for a further 3 days. The hair follicles are then washed with phosphate-buffered saline solution in order to remove non-incorporated radioactivity and the DNA is solubilized by incubation with alkali overnight. The radioactivity incorporated into the follicular DNA is then measured using a liquid scintillation counter.

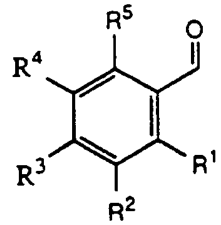
The incubation of mouse hair follicles with the compound of Example 1 results in a stimulation of the cell proliferation with a maximum DNA synthesis value of 211 ± 17% (compared with controls) at a concentration of 0.3 µM. The concentration which resulted in a half-maximum stimulation of the DNA synthesis (EC_{50} value) was 0.1 µM. The activity of the compound of Example 1 in this culture system exceeded that of known hypotrichotic agents. For example, minoxidil stimulates hair follicle DNA synthesis to 160 ± 15% (compared with controls) and has a EC_{50} value of 200 µM.

In accordance with the invention the compounds of formula I and their pharmaceutically usable salts can be manufactured in accordance with the invention by reacting a diketone of the general formula



(II)

wherein R^6, R^7 and R^8 have the above significance, with an aldehyde of the general formula



(III)

wherein R^1, R^2, R^3, R^4 and R^5 have the significance given above and wherein a hydroxy group in the compounds of formulae II and III can be present in protected form,

in the presence of ammonia, cleaving off a hydroxy protecting group which may be present and, if desired, functionally modifying reactive groups present in a compound of formula I obtained and, if desired, converting a compound of formula I into a pharmaceutically usable salt.

The reaction of a diketone of formula II with an aldehyde of formula III and with ammonia can be carried out in a manner known per se. For example, a diketone of formula II can be reacted with an aldehyde of formula III and with ammonium acetate (a reagent which liberates ammonia) in an organic acid such as acetic acid at an elevated temperature, e.g. at about 50 to about 100°C.

Hydroxy groups in the compounds of formulae II and/or III can be present in the reaction in accordance with the invention in protected form, for example as a benzyl ether, which can be removed from the reaction product in a manner known per se, in the case of the benzyl ether by e.g. catalytic hydrogenation.

The diketones of formula II and aldehydes of formula III are known or can be prepared in a manner known per se as described in the Examples or in analogy thereto.

Functional modification of reactive groups can comprise e.g. the saponification of ester groups, the reduction of nitro groups to amino groups and the alkylation of amino groups. These functional modifications can be carried out in a manner known per se, e.g. as described in the Examples or in analogy thereto.

Acidic compounds of formula I can be converted into pharmaceutically usable salts by treatment with bases and basic compounds of formula I can be converted into pharmaceutically usable salts by treatment with acids. Such reactions can be carried out in a manner known per se.

The compounds of formula I and their salts can be used as medicaments, e.g. in the form of pharmaceutical preparations.

The medicaments can be administered enterally, parenterally or topically. Medicaments in the form of tablets, capsules, dragées, syrups, suspensions, solutions and suppositories are e.g. suitable for enteral administration. Medicaments in the form of infusion or injection solutions are suitable for parenteral administration.

The dosages in which the preparations are administered can vary according to the mode of use and route of use as well as according to the requirements of the patient.

In the case of the oral administration of the compounds in accordance with the invention there come into consideration in the case of adults dosages of about 0.1-100 mg/kg, preferably 0.5-50 mg/kg, per day.

The preparations can be administered in one or more doses. Capsules containing about 5-500 mg of active ingredient comprise a preferred administration form.

The preparations can contain inert or pharmacodynamically active additives. Tablets or granulates e.g. can contain a series of binders, fillers, carriers or diluents. Liquid preparations can be present, for example, in the form of a sterile water-miscible solutions. Capsules can contain a filler or thickener in addition to the active ingredient. Furthermore, flavour-improving additives as well as substances usually used as preservatives, stabilizers, moisturizers and emulsifiers as well as salts for

varying the osmotic pressure, buffers and other additives can be present.

The previously mentioned carriers and diluents can comprise organic or inorganic substances, e.g. water, gelatine, lactose, starch, magnesium stearate, talc, gum arabic, polyalkylene glycols and the like. It is a prerequisite that all adjuvants used in the production of the preparations are non-toxic.

For topical application the active ingredients are conveniently used in the form of salves, tinctures, creams, solutions, lotions, sprays, suspensions, gels and the like. Salves and creams as well as solutions are preferred. These preparations adapted for topical application can be produced by mixing the process products as active ingredients with non-toxic, inert solid or liquid carriers which are suitable for topical treatment and which are customary in such preparations.

For topical application there are conveniently suitable about 0.1-10%, preferably 0.3-2%, solutions as well as about 0.1-10%, preferably about 0.3-2%, salves and creams.

If desired, an antioxidant, e.g. tocopherol, N-methyl-γ-tocopheramine as well as t-butyl-hydroxyanisole or t-butyl-hydroxytoluene, can be admixed with the preparations.

The following Examples illustrate the invention in more detail.

Example 1

A mixture of 12.3 g of 1-(4-chlorophenyl)-2-pyridin-4-yl-ethanedione and 7.4 g of 2,4,6-trimethylbenzaldehyde in 125 ml of acetic acid containing 40 g of ammonium acetate was stirred at 100°C for 2 hours, then left to cool to room temperature. The mixture was poured into a mixture of 300 ml of ice-water and 200 ml of concentrated ammonia solution and the mixture was

extracted three times with ethyl acetate. After drying over anhydrous magnesium sulphate the solvent was evaporated. The residue was purified by chromatography on silica gel with dichloromethane/methanol (9:1) and crystallized from ethyl acetate to yield 6.7 g of 4-[5-(4-chlorophenyl)-2-(2,4,6-trimethyphenyl)imidazol-4-yl]pyridine, m.p. 275°C.

Examples 2-63

The following compounds were prepared in analogy to Example 1:

2. 4-[5-(3-Chlorophenyl)-2-(2,4,6-trimethylphenyl)imidazol-4-yl]pyridine, m.p. 235-237°C (dichloromethane/hexane),
3. 4-[5-(3,4-dichlorophenyl)-2-(2,4,6-trimethylphenyl)-imidazol-4-yl]pyridine, m.p. 252-254°C (dichloromethane/diethyl ether),
4. 4-[5-(4-fluorophenyl)-2-(2,4,6-trimethylphenyl)imidazol-4-yl]pyridine, m.p. 252-254°C (diethyl ether),
5. 4-[5-(4-chlorophenyl)-2-(2,6-dichlorophenyl)imidazol-4-yl]pyridine, m.p. >280°C (ethanol),
6. 4-[5-(2,4-dichlorophenyl)-2-(2,6-dichlorophenyl)imidazol-4-yl]pyridine, m.p. 270-272°C (ethyl acetate/hexane),
7. 4-[5-(4-chlorophenyl)-2-(2,6-dimethylphenyl)imidazol-4-yl]pyridine, m.p. 290-292°C (ethyl acetate/hexane),
8. 4-[5-(4-chlorophenyl)-2-(2,3,4,5,6-pentamethylphenyl)-imidazol-4-yl]pyridine, m.p. >280°C (ethanol),
9. 4-[5-(2-fluorophenyl)-2-(2,4,6-trimethylphenyl)imidazol-4-yl]pyridine, m.p. >260°C (hexane),
10. 4-[5-(3-methoxyphenyl)-2-(2,4,6-trimethylphenyl)-imidazol-4-yl]pyridine, m.p. >260°C (diethyl ether/hexane),
11. 4-[5-(3-bromophenyl)-2-(2,4,6-trimethylphenyl)imidazol-4-yl]pyridine, m.p. 248-250°C (ethyl acetate/hexane),
12. 4-[5-(4-chlorophenyl)-2-(2,6-dibromophenyl)imidazol-4-yl]pyridine, m.p. >260°C (diethyl ether),
13. 4-[5-(3-methylphenyl)-2-(2,4,6-trimethylphenyl)imidazol-4-yl]pyridine, m.p. 251-253°C (diethyl ether),
14. 4-[5-(4-chlorophenyl)-2-(2-chloro-6-methylphenyl)-

imidazol-4-yl]pyridine, m.p. >260°C (acetone),
15. 4-[5-(4-chlorophenyl)-2-(2-chloro-6-nitrophenyl)imidazol-4-yl]pyridine, m.p. >260°C (ethyl acetate/hexane),
16. 4-[5-(4-chlorophenyl)-2-(2-methyl-6-nitrophenyl)-imidazol-4-yl]pyridine, m.p. >260°C (acetone/hexane),
17. 4-[5-(4-chlorophenyl)-2-(2-chloro-6-fluorophenyl)-imidazol-4-yl]pyridine, m.p. 285°C (ethyl acetate),
18. 4-[5-(3-chlorophenyl)-2-(2-chloro-6-nitrophenyl)imidazol-4-yl]pyridine, m.p. 259-260°C (acetone/hexane),
19. 4-[5-(3,4-dichlorophenyl)-2-(2-chloro-6-nitrophenyl)-imidazol-4-yl]pyridine, m.p. >260°C (ethyl acetate/hexane),
20. 4-[5-(4-fluorophenyl)-2-(2-chloro-6-nitrophenyl)imidazol-4-yl]pyridine, m.p. >260°C (acetone/hexane),
21. 4-[5-(4-chlorophenyl)-2-(2-bromo-6-methylphenyl)-imidazol-4-yl]pyridine, m.p. >260°C (acetone/hexane),
22. 4-[5-(4-bromophenyl)-2-(2-chloro-6-nitrophenyl)imidazol-4-yl]pyridine, m.p. >260°C (acetone/hexane),
23. 4-[5-(4-chlorophenyl)-2-(2,3,5,6-tetramethylphenyl)-imidazol-4-yl]pyridine, m.p. >260°C (acetone),
24. 4-[5-(4-chlorophenyl)-2-(2-bromo-6-chlorophenyl)-imidazol-4-yl]pyridine, m.p. >260°C (acetone),
25. 4-[5-(3-bromophenyl)-2-(2-chloro-6-nitrophenyl)imidazol-4-yl]pyridine, m.p. 238-239°C (acetone/hexane),
26. 4-[5-(3-methoxyphenyl)-2-(2-chloro-6-nitrophenyl)-imidazol-4-yl]pyridine, m.p. 232-234°C (tetrahydrofuran/hexane),
27. 4-[5-(4-chlorophenyl)-2-(2,6-diisopropylphenyl)imidazol-4-yl]pyridine, m.p. >260°C (acetone/hexane),
28. 4-[5-(4-fluorophenyl)-2-(2-bromo-6-methylphenyl)-imidazol-4-yl]pyridine, m.p. >260°C (dichloromethane),
29. 4-[5-(4-chlorophenyl)-2-(2-bromo-3-methylphenyl)-imidazol-4-yl]pyridine, m.p. >260°C (diethyl ether),
30. 4-[5-(4-fluorophenyl)-2-(2-methyl-6-nitrophenyl)-imidazol-4-yl]pyridine, m.p. >250°C (dichloromethane/hexane),
31. 4-[5-(4-chlorophenyl)-2-(2-bromophenyl)imidazol-4-yl]pyridine, m.p. 206-208°C (ethyl acetate/hexane),
32. 4-[5-(3-bromophenyl)-2-(2-bromophenyl)imidazol-4-yl]pyridine, m.p. 141-143°C (ethyl acetate/hexane),
33. dimethyl-[2-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-

2-yl]-3-methylphenyl]amine, m.p. 230-232°C (diethyl ether/hexane),

34. methyl 3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzoate, m.p. 228°C (ethyl acetate/isopropyl ether),

35. 4-[2-(3-bromo-2,6-dimethylphenyl)-5-(4-chlorophenyl)-imidazol-4-yl]pyridine, m.p. 300-305°C (ethyl acetate),

36. 4-[5-(4-chlorophenyl)-2-(2,6-dimethyl-3-nitrophenyl)-imidazol-4-yl]pyridine, m.p. 295-298°C (ethyl acetate/hexane),

37. 4-[5-(4-chlorophenyl)-2-(2-fluoro-6-trifluoromethyl-phenyl)imidazol-4-yl]pyridine, m.p. 264-266°C (acetone/hexane),

38. 4-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]morpholine, m.p. 239-240°C (ethyl acetate),

39. 4-[5-(4-chlorophenyl)-2-(2-allyl-6-methylphenyl)-imidazol-4-yl]pyridine, m.p. 96-98°C,

40. [3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]dimethylamine, m.p. 222°C (acetonitrile),

41. 4-[5-(4-chlorophenyl)-2-(2-methoxymethyl-6-methyl-phenyl)imidazol-4-yl]pyridine, m.p. 138-140°C (acetone/hexane),

42. 4-[5-(4-chlorophenyl)-2-(3-methoxy-2,6-dimethylphenyl)-imidazol-4-yl]pyridine, m.p. 283-285°C (ethyl acetate),

43. 4-[5-(4-chlorophenyl)-2-(2,6-dimethyl-3,5-dinitrophenyl)-imidazol-4-yl]pyridine, m.p. 300-305°C,

44. 4-[5-(4-chlorophenyl)-2-(2-chloro-6-trifluoromethyl-phenyl)imidazol-4-yl]pyridine, m.p. >260°C (acetone/hexane),

45. 1-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]-4-methylpiperazine, m.p. 280°C (ethyl acetate),

46. 3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4-dimethylphenol, m.p. >300°C (ethanol),

47. 4-[4-(4-chlorophenyl)-5-pyridin-4-yl-imidazol-2-yl]-3,5-dimethylphenol, m.p. 189-191°C (dichloromethane/diethyl ether),

48. ethyl 1-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]piperidin-4-carboxylate, m.p. 210°C (ethyl acetate),

49. ethyl [4-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-3,5-dimethylphenoxy]acetate, m.p. 210-211°C (tetrahydro-

furan/hexane),

50. 4-[2-(3-azidomethyl-2,4,6-trimethylphenyl)-5-(4-chlorophenyl)imidazol-4-yl]pyridine, m.p. 230°C (ethyl acetate),

51. [3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylphenyl]acetonitrile, m.p. 250°C (acetonitrile),

52. 3-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4-dimethylphenoxy]propan-1-ol, m.p. 260-263°C (ethyl acetate),

53. [3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-benzyl]diethylamine, m.p. 142°C (ethyl acetate),

54. 4-[5-(4-chlorophenyl)-2-(2,4,6-trimethyl-3-nitrophenyl)-imidazol-4-yl]pyridine, m.p. 295-299°C (methanol/ethyl acetate),

55. 4-[5-(4-chlorophenyl)-2-(2,3,6-trichlorophenyl)imidazol-4-yl]pyridine, m.p. >260°C (acetone/hexane),

56. 4-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-3,5-dimethylphenoxy]acetamide, m.p. >260°C (water),

57. [3-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4-dimethylphenoxy]propyl]dimethylamine, m.p. 145-149°C (ethyl acetate/isopropyl ether/hexane),

58. 3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylphenol, m.p. >300°C (ethanol),

59. (2RS,6RS)- and (2R,6S)-4-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]-2,6-dimethylmorpholine, m.p. 163-170°C (ethyl acetate),

60. 4-[5-(4-chlorophenyl)-2-(2,4,6-trimethyl-3-piperidin-1-yl-methylphenyl)-imidazol-4-yl]pyridine, m.p. 156-165°C (ethyl acetate/hexane),

61. (S)-[1-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]pyrrolidin-2-yl]methanol, m.p. 165-168°C (ethyl acetate/hexane),

62. 3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4-dimethylbenzyl acetate, m.p. 232-234°C (ethyl acetate/isopropyl ether),

63. 3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl acetate, m.p. 234-236°C (ethyl acetate/hexane).

Example 64

(i) 4-[5-(3-Benzyloxyphenyl)-2-(2,4,6-trimethylphenyl)-imidazol-4-yl]pyridine, m.p. 247-248°C (ethyl acetate/hexane) was prepared in analogy to Example 1 from 1-(3-benzyloxy-phenyl)-2-pyridin-4-yl-ethanedione, m.p. 79-80°C (dichloro-methane/hexane).

(ii) . A solution of 4.4 g of 4-[5-(3-benzyloxyphenyl)-2-(2,4,6-trimethylphenyl)imidazol-4-yl]pyridine in 500 ml of methanol was hydrogenated in the presence of 0.4 g of 10% palladium-on-charcoal for 3 hours. The catalyst was filtered off and the solution was evaporated. Recrystallization of the residue from ethyl acetate/hexane yielded 3.0 g of 3-[4-pyridin-4-yl-2-(2,4,6-trimethylphenyl)imidazol-5-ylphenol, m.p. 338-340°C.

Example 65

(i) 4-[5-(2-Benzyloxymethyl)phenyl-2-(2,4,6-trimethyl-phenyl)imidazol-4-yl]pyridine, m.p. 125-127°C (diethyl ether), was prepared in analogy to Example 1 from 1-(2-benzyloxy-phenyl)-2-pyridin-4-yl-ethanedione.

(ii) A solution of 1.0 g of 4-[5-(2-benzyloxymethyl)phenyl-2-(2,4,6-trimethylphenyl)imidazol-4-yl]pyridine in 40 ml of acetic acid was hydrogenated in the presence of 0.1 g of 10% palladium/charcoal for 3 hours. The catalyst was filtered off and the solution was poured into a mixture of 200 g of ice and 150 ml of concentrated ammonium hydroxide. The solid was filtered off and dissolved in dichloromethane. After drying over anhydrous mag-nesium sulphate the solvent was evaporated and the residue was recrystallized from tetrahydrofuran/hexane. 0.3 g of 2-[4-pyridin-4-yl-2-(2,4,6-trimethylphenyl)imidazol-5-yl]phenyl-methanol, m.p. 215-217°C, was obtained.

Example 66

A solution of 0.2 g of 4-[5-(4-chlorophenyl)-2-(2-chloro-6-nitrophenyl)imidazol-4-yl]pyridine in 20 ml of methanol was hydrogenated in the presence of 0.1 g of 10% palladium/charcoal for 2 hours. The catalyst was filtered off and the solution was evaporated to dryness. Recrystallization from ethyl acetate yielded 0.1 g of 3-chloro-2-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]phenylamine, m.p. 220-222°C.

Example 67

A solution of 480 mg of 4-[5-(4-chlorophenyl)-2-(2,6-dimethyl-3-nitrophenyl)imidazol-4-yl]pyridine in 100 ml of methanol was hydrogenated in the presence of 35 mg of platinum oxide for 2 hours. The catalyst was filtered off and the solvent was evaporated. Recrystallization from acetonitrile yielded 280 mg of 3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4-dimethylphenylamine, m.p. 302-306°C.

Example 68

A solution of 90 mg of sodium in 70 ml of methanol was treated with 1.95 g of 3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl acetate. The mixture was stirred at room temperature for 3 hours, then treated with 0.3 ml of acetic acid. The solvent was evaporated and the residue was crystallized from ethyl acetate to yield 1.1 g of 3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylphenyl)methanol, m.p. 282-285°C.

Example 69

[3-[5-(4-Chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4-dimethylphenyl)methanol, m.p. >300°C, was prepared in analogy to Example 67 from 3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4-dimethylbenzyl acetate.

Example 70

A solution of 0.63 g of 4-[5-(4-chlorophenyl)-2-(2,4,6-trimethyl-3-nitrophenyl)imidazol-4-yl]pyridine in 100 ml of methanol was was hydrogenated in the presence of 0.8 g of platinum oxide for 24 hours. The catalyst was filtered off and the solution was evaporated. The residue was chromatographed on silica gel using dichloromethane/methanol as the eluent. Recrystallization from methanol/water yielded 0.14 g of 3-[5-(4-chlorophenyl)-4-pyridin-4-yl)imidazol-2-yl]-2,4,6-trimethyl-phenylamine, m.p. >300°C.

The starting materials which are used in Example 1-70, the preparation of which has not hitherto been described, can be prepared as described hereinafter or in analogy thereto:

A. Ethanone derivatives (compounds of formula II)

1-(4-Chlorophenyl)-2-pyridin-4-yl-ethanedione

(i) 19.4 g of 4-pyridylmethyl isocyanide were added dropwise at -5°C while stirring to a solution of 37.8 g of potassium tert-butylate in 400 ml of tetrahydrofuran. The mixture was then treated with 23.1 g of 4-chlorobenzaldehyde and stirred at -5°C for a further 2 hours. Thereafter, 19.7 g of acetic acid were added dropwise at 0°C while stirring and the solid was filtered off. The residue was chromatographed on silica gel with dichloromethane/methanol (95:5) as the eluent and recrystallized from dichloromethane/hexane. 25.0 g of (E/Z)-N-[2-(4-chloro-phenyl)-1-pyridin-4-yl-vinyl]formamide, m.p. 155-156°C, were obtained.

(ii) A solution of 39.0 g of (E/Z)-N-[2-(4-chlorophenyl)-1-pyridin-4-yl-vinyl]formamide in 430 ml of methanol was treated at 0°C with 112 ml of concentrated hydrochloric acid. The mixture was stirred at 32-34°C for 16 hours. The mixture was then cooled to 0°C and added dropwise while stirring at 0°C to a solution of 82.2 g of potassium hydroxide in 100 ml of water.

The solid was filtered off and recrystallized from dichloromethane/hexane. 25.0 g of 1-(4-chlorophenyl)-2-pyridin-4-yl-ethanone, m.p. 85-86°C, were obtained.

(iii) A solution of 25 g of 1-(4-chlorophenyl)-2-pyridin-4-yl-ethanone in 285 ml of dioxan was treated with 20 g of selenium dioxide. The mixture was stirred at 100°C for 1 hour and filtered. The solvent was evaporated and the residue was dissolved in dichloromethane. The solution was washed three times with water, dried over anhydrous magnesium sulphate and evaporated. The residue was dissolved in ethyl acetate, the solution was filtered over silica gel and evaporated to yield 23.7 g of 1-(4-chlorophenyl)-2-pyridin-4-yl-ethanedione, m.p. 119-120°C.

B. Benzaldehyde derivatives (compound of formula III)

2-Bromo-6-methylbenzaldehyde

(i) A solution of 9.52 g of (2-bromobenzylidene)phenylamine in 150 ml of acetic acid was treated with 7.9 g of palladium(II) acetate. The mixture was heated to reflux for 1 hour, then poured into 150 ml of water and extracted three times with dichloromethane. The combined organic extracts were washed with water, dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was chromatographed on silica gel with dichloromethane/methanol (99:1) as the eluent and yielded 10.3 g of bis[acetato(3-bromo-2-phenyliminomethyl-phenyl)palladium](Pd-Pd), m.p. 199-200°C.

(ii) A solution of 10.3 g of bis[acetato(3-bromo-2-phenyliminomethylphenyl)palladium](Pd-Pd) in 80 ml of dichloromethane and 80 ml of acetone was treated with 90 ml of saturated sodium chloride solution while stirring. After 10 minutes the solid was filtered off and yielded 6.1 g of bis[chloro(3-bromo-2-phenyliminomethylphenyl)palladium](Pd-Pd), m.p. 280-282°C.

(iii) A solution of 6.1 g of bis[chloro(3-bromo-2-phenyliminomethylphenyl)palladium](Pd-Pd) in 225 ml of absolute benzene

was treated with 7.9 g of triphenylphosphine under argon. Thereafter, the mixture was stirred at room temperature for a further 30 minutes. 12.5 ml of a 1.6M solution of methyllithium in diethyl ether was added dropwise at 0°C while stirring and the mixture was thereafter stirred at room temperature for 1 hour. The mixture was then treated at 0°C with 225 ml of 1N hydrochloric acid, filtered and the solid was washed with diethyl ether. The combined organic extracts were washed twice with water, dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was chromatographed on silica gel with hexane/ethyl acetate (98:2) as the eluent and yielded 0.7 g of 2-bromo-6-methylbenzaldehyde, m.p. 48-49°C.

2,6-Diisopropylbenzaldehyde

6.8 ml of a 1.6M solution of butyllithium in hexane was added dropwise at -78°C while stirring to a solution of 2.6 g of 2-bromo-1,3-diisopropylbenzene in 16 ml of tetrahydrofuran. The mixture was stirred at the same temperature for 30 minutes and thereafter treated with a solution of 1.3 g of N-formylpiperidine in 1.5 ml of tetrahydrofuran. Thereafter, the mixture was left to warm to room temperature over a period of 6 hours. The mixture was cooled to 0°C and treated with 12 ml of 3N hydrochloric acid. The aqueous solution was extracted four times with diethyl ether and the combined organic extracts were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was chromatographed on silica gel with dichloromethane as the eluent and yielded 1.07 g of 2,6-diisopropylbenzaldehyde as an oil.

2-Dimethylamino-6-methylbenzaldehyde

(i) A solution of 3 g of 2-amino-6-methylbenzoic acid in 30 ml of acetic acid and 15 ml of 33% formaldehyde was hydrogenated at room temperature for 22 hours in the presence of 1 g of 10% palladium/charcoal. The catalyst was filtered off and the solution was evaporated to dryness. The residue was treated

with 200 ml of methanol and the mixture was stirred at 50°C for 20 minutes, cooled to -20°C and filtered. The solvent was evaporated and the residue was chromatographed on silica gel with dichloromethane/methanol (95:5) as the eluent. 1.5 g of 2-dimethylamino-6-methylbenzoic acid, m.p. 117-119°C, were obtained.

(ii) A solution of 1.3 g of 2-dimethylamino-6-methylbenzoic acid in 15 ml of tetrahydrofuran was added dropwise while stirring at room temperature to a suspension of 0.5 g of lithium aluminium hydride in 15 ml of tetrahydrofuran. The mixture was stirred at room temperature for a further 4 hours. Thereafter, the mixture was treated in succession with 15 ml of 50% ammonium chloride solution and 5 ml of water at 10°C while stirring, filtered and extracted twice with dichloromethane. The combined organic solutions were dried over anhydrous magnesium sulphate and evaporated to yield 0.8 g 2-dimethylamino-6-methylbenzyl alcohol as an oil.

(iii) A solution of 1.5 g of 2-dimethylamino-6-methylbenzyl alcohol in 7 ml of dichlormethane was added dropwise at room temperature while stirring to a suspension of 2.88 g of pyridinium chlorochromate in 12 ml of dichloromethane. Thereafter, the mixture was stirred at room temperature for a further 18 hours, treated with 50 ml of diethyl ether, filtered over Florisil and the residue was washed twice with 50 ml portions of diethyl ether. The combined organic extracts were evaporated and the residue was chromatographed on silica gel with diethyl ether/hexane (1:4) as the eluent. 0.5 g of 2-dimethylamino-6-methylbenzaldehyde was obtained as an oil.

2,6-Dimethyl-3,5-dinitrobenzaldehyde and 2,6-dimethyl-3-nitrobenzaldehyde

2 g of 2,6-dimethylbenzaldehyde were added at room temperature over a period of 15 minutes to a mixture of 20 ml of concentrated nitric acid and 10 ml of acetic acid. Thereafter, the mixture was stirred at room temperature for 5 minutes and

poured on to ice-water. The mixture was stirred for a further 5 minutes, filtered and the residue was dissolved in dichloromethane. After drying over anhydrous magnesium sulphate the solvent was evaporated. The residue was chromatographed on silica gel with hexane/ethyl acetate as the eluent and yielded 1.23 g of 2,6-dimethyl-3-nitrobenzaldehyde, m.p. 54-57°C (from hexane), and 0.33 g of 2,6-dimethyl-3,5-dinitrobenzaldehyde, m.p. 119-122°C (from toluene/hexane).

2,4,6-Trimethyl-3-morpholin-4-yl-methylbenzaldehyde

A solution of 0.98 g of 3-chloromethyl-2,4,6-trimethylbenzaldehyde in 20 ml of acetonitrile was treated with 0.87 ml of morpholine. The mixture was stirred at room temperature for 4 hours and thereafter filtered. The solvent was evaporated and the residue was dissolved in ethyl acetate. The solution was washed twice with water, dried over anhydrous magnesium sulphate and evaporated to dryness. Distillation of the residue yielded 1.05 g of 2,4,6-trimethyl-3-morpholin-4-yl-methylbenzaldehyde, b.p. 150°C/0.3 Torr.

2-Allyl-6-methylbenzaldehyde

(i) 38 ml of a 1M solution of vinylmagnesium bromide in tetrahydrofuran were added over a period of 5 minutes while stirring and under an argon atmosphere at 0-5°C to a mixture of 7.1 g of 2-bromo-1-bromomethyl-3-methylbenzene, 0.51 g of copper(I) iodide and 0.42 g of 2,2-bipyridyl in 20 ml of benzene. The temperature rose to 42°C. Thereafter, the mixture was stirred at room temperature overnight. The mixture was then treated in succession with 183 ml of saturated ammonium chloride solution and 2 ml of concentrated ammonium hydroxide solution at 0°C while stirring and extracted four times with diethyl ether. The combined organic extracts were washed in succession with 1N hydrochloric acid, saturated sodium hydrogen carbonate solution and water, dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was purified on silica gel with

cyclohexane/dichloromethane (99:1) and yielded 3.1 g of 1-allyl-2-bromo-3-methylbenzene as an oil.

(ii) A solution of 2.3 g of 1-allyl-2-bromo-3-methylbenzene in 10 ml of tetrahydrofuran was added dropwise at 0°C while stirring to a suspension of 0.287 g of magnesium in 10 ml of tetrahydrofuran. Thereafter, the mixture was heated to reflux for 2 hours and finally left to cool to 0°C. Thereafter, a mixture of 1 ml of N,N-dimethylformamide and 5 ml of tetrahydrofuran was added dropwise at 0°C while stirring. After further stirring at 0°C for 2 hours and at room temperature overnight the mixture was again left to cool to 0°C and heated in succession with 80 ml of saturated ammonium chloride solution and 2 ml of concentrated ammonium hydroxide solution. The mixture was thereafter extracted four times with diethyl ether and the combined organic extracts were washed in succession with 1N hydrochloric acid, saturated sodium hydrogen carbonate solution and water, dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was purified on silica gel with dichloromethane/hexane (1:1) as the eluent and yielded 6.2 g of 2-allyl-6-methylbenzaldehyde as an oil.

3-Dimethylaminomethyl-2,4,6-trimethylbenzaldehyde

3-Dimethylaminomethyl-2,4,6-trimethylbenzaldehyde, b.p. 150°C/0.3 Torr, was prepared in analogy to the procedure described above for the preparation of 2,4,6-trimethyl-3-morpholin-4-yl-methylbenzaldehyde.

2-Methoxymethyl-6-methylbenzaldehyde

i) A solution of 14.7 g of 2-bromo-1-bromomethyl-3-methylbenzene in 100 ml of acetic acid was treated with 5.2 g of anhydrous sodium acetate and heated to reflux overnight. The mixture was evaporated to dryness and the residue was extracted with dichloromethane. The extract was evaporated to dryness and the residue was chromatographed on silica gel with dichloro-

methane/hexane (1:1) as the eluent. 10.1 g of 2-bromo-3-methylbenzyl acetate were obtained as an oil.

(ii) A solution of 10.1 g of 2-bromo-3-methylbenzyl acetate in 75 ml of ethanol was treated with a solution of 13 g of potassium hydroxide in 25 ml of water and the mixture was heated to reflux overnight. The mixture was then left to cool to room temperature, acidified with 3N hydrochloric acid and extracted three times with dichloromethane. The combined organic extracts were washed with water, dried over anhydrous magnesium sulphate and evaporated. The residue was chromatographed on silica gel with dichloromethane as the eluent and yielded 6.9 g of 2-bromo-3-methylbenzyl alcohol, m.p. 80-81°C.

(iii) A solution of 2.01 g of 2-bromo-3-methylbenzyl alcohol in 10 ml of tetrahydrofuran was added dropwise at 0°C while stirring to a suspension of 0.48 g of 55-65% sodium hydride in 12 ml of tetrahydrofuran. The mixture was stirred at 0°C for a further 30 minutes and treated with 0.75 ml of methyl iodide. After stirring at 4°C for 30 minutes and at room temperature for 40 minutes the mixture was again cooled to 0°C, treated with 2 ml of water and poured into 40 ml of diethyl ether. The organic solution was washed with 30 ml of saturated sodium chloride solution, dried over anhydrous magnesium sulphate and evaporated to yield 2.0 g of 2-bromo-1-methoxymethyl-3-methylbenzene as an oil.

(iv) 5.9 ml of a 1.6M solution of butyllithium in hexane were added dropwise at -78°C while stirring to a solution of 2.0 g of 2-bromo-1-methoxymethyl-3-methylbenzene in 13 ml of tetrahydrofuran. Thereafter, a solution of 0.75 ml of N,N-dimethylformamide in 1 ml of tetrahydrofuran was added at the same temperature. After the temperature had increased slowly to -10°C the mixture was treated with 10 ml of 3N hydrochloric acid and poured into 30 ml of diethyl ether. The aqueous solution was extracted twice with diethyl ether and the combined organic extracts were washed with 30 ml of saturated sodium chloride solution, dried over anhydrous magnesium sulphate and evapor-

ated. 1.5 g of 2-methoxymethyl-6-methylbenzaldehyde were obtained as an oil.

3-Methoxy-2,6-dimethylbenzaldehyde

i) 30.3 ml of a 1.2M solution of diisobutylaluminium hydride in toluene were added at 10°C while stirring over a period of 10 minutes to a solution of 2.8 g of methyl 3-methoxy-2,6-dimethylbenzoate in 50 ml of tetrahydrofuran. The mixture was stirred at room temperature for 30 minutes, then cooled to 0°C and treated in succession at 0°C while stirring with 5 ml of ethyl acetate and 50 ml of 1N hydrochloric acid. The mixture was stirred at room temperature for 15 minutes and extracted twice with ethyl acetate. After drying over anhydrous magnesium sulphate the solvent was evaporated and the residue was crystallized from hexane. 1.9 g of 2,6-dimethyl-3-methoxybenzyl alcohol, m.p. 88-89°C, were obtained.

(ii) A solution of 1.9 g of 2,6-dimethyl-3-methoxybenzyl alcohol in 70 ml of dichloromethane was treated with 9.9 g of manganese dioxide and stirred at room temperature for 18 hours. The mixture was filtered and the solvent was evaporated. The residue was chromatographed on silica gel with hexane/ethyl acetate (9:1) as the eluent and yielded 0.7 g of 3-methoxy-2,6-dimethylbenzaldehyde, m.p. 59-64°C.

2,4,6-Trimethyl-3-(4-methylpiperazin-1-yl-methyl)-benzaldehyde

2,4,6-Trimethyl-3-(4-methylpiperazin-1-yl-methyl)-benzaldehyde, m.p. 90°C (from acetonitrile), was prepared in analogy to the manner described above for the preparation of 2,4,6-trimethyl-3-morpholin-4-yl-methylbenzaldehyde.

3-Hydroxy-2,6-dimethylbenzaldehyde

(i) A solution of 2.8 g of 2,6-dimethyl-3-nitrobenzaldehyde in 150 ml of toluene was treated with 5 ml of ethylene glycol and

20 mg of p-toluenesulphonic acid. The mixture was heated to reflux for 18 hours, with the water being separated using a separator. The mixture was left to cool to room temperature and was washed twice with water. After drying over anhydrous magnesium sulphate the solvent was evaporated and the crystalline residue was crystallized from hexane. 3.0 g of 2-(2,6-dimethyl-3-nitrophenyl)-1,3-dioxolane, m.p. 69-71°C, were obtained.

(ii) A solution of 2.7 g of 2-(2,6-dimethyl-3-nitrophenyl)-1,3-dioxolane in 30 ml of ethyl acetate was hydrogenated in the presence of 0.2 g of platinum oxide for 45 minutes. The catalyst was filtered off and the solution was concentrated to a crystalline residue. Recrystallization from hexane yielded 2.35 g of 2-(3-amino-2,6-dimethylphenyl)-1,3-dioxolane, m.p. 100-103°C.

(iii) A solution of 0.73 g of sodium nitrite in 2 ml of water was added at 0°C over a period of 15 minutes while stirring to a suspension of 2.0 g of 2-(3-amino-2,6-dimethylphenyl)-1,3-dioxolane in 1.9 ml of concentrated sulphuric acid and 5.5 ml of water. Thereafter, the mixture was stirred at room temperature for 15 minutes and then added while stirring over a period of 5 minutes at 110°C to a mixture of 1 ml of concentrated sulphuric acid and 15 ml of water. The mixture was heated to reflux while stirring for 1 hour, then left to cool to room temperature, filtered and washed with water to yield 1.55 g of 3-hydroxy-2,6-dimethylbenzaldehyde, m.p. 159-165°C (from isopropyl ether).

Ethyl 1-(3-formyl-2,4,6-trimethylbenzyl)piperidine-4-carboxylate

Ethyl 1-(3-formyl-2,4,6-trimethylbenzyl)piperidine-4-carboxylate, m.p. 78°C (from hexane), was obtained in analogy to the preparation of 2,4,6-trimethyl-3-morpholin-4-yl-methylbenzaldehyde described above.

(4-Formyl-3,5-dimethylphenoxy)acetate

A mixture of 0.7 g of 4-hydroxy-2,6-dimethylbenzaldehyde, 2.4 g of ethyl bromoacetate and 2.1 g of anhydrous potassium carbonate in 10 ml of acetone was heated to reflux for 2 hours, thereafter filtered and evaporated. Recrystallization of the residue from hexane yielded 0.7 g of ethyl (4-formyl-3,5-dimethylphenoxy)acetate, m.p. 78-80°C.

3-Azidomethyl-2,4,6-trimethylbenzaldehyde

A solution of 9.8 g of 3-chloromethyl-2,4,6-trimethylbenzaldehyde in 125 ml of dimethyl sulphoxide was treated with 3.8 g of sodium azide, the mixture was stirred at room temperature for 3 hours and the solvent was evaporated. The residue was dissolved in ethyl acetate and the solution was washed with water. After drying over anhydrous magnesium sulphate the solvent was removed and 9.1 g of 3-azidomethyl-2,4,6-trimethylbenzaldehyde, m.p. 60°C, were obtained.

(3-Formyl-2,4,6-trimethylphenyl)acetonitrile

A solution of 9.8 g of 3-chloromethyl-2,4,6-trimethylbenzaldehyde in 500 ml of ethanol/water (1:1) was treated with 3.6 g of potassium cyanide. The mixture was stirred at room temperature for 18 hours and the solvent was evaporated. The residue was dissolved in ethyl acetate and the solution was washed with water. After drying over anhydrous magnesium sulphate the solvent was evaporated and the residue was crystallized from isopropyl ether. 4.8 g of (3-formyl-2,4,6-trimethylphenyl)acetonitrile, m.p. 83°C, were obtained.

3-(3-Hydroxypropoxy)-2,6-dimethylbenzaldehyde

A suspension of 1.5 g of 3-hydroxy-2,6-dimethylbenzaldehyde in 15 ml of water was treated with 0.4 g of sodium hydroxide and 0.87 ml of 3-bromo-2-propanol. The solution was stirred at 100°C for 18 hours and thereafter cooled to room

temperature. The solution was extracted three times with dichloromethane and the combined organic extracts were washed three times with water. After drying over anhydrous magnesium sulphate the solvent was evaporated. The residue was chromatographed on silica gel with ethyl acetate/hexane as the eluent and subsequently recrystallized from isopropyl ether/hexane. 0.9 g of 3-(3-hydroxypropoxy)-2,6-dimethylbenzaldehyde, m.p. 68-70°C, was obtained.

3-Diethylaminomethyl-2,4,6-trimethylbenzaldehyde

3-Diethylaminomethyl-2,4,6-trimethylbenzaldehyde, b.p. 200°C/0.2 Torr, was prepared in analogy to the procedure described for the synthesis of 2,4,6-trimethyl-3-morpholin-4-yl-methylbenzaldehyde.

2-(4-Formyl-3,5-dimethylphenoxy)acetamide

A solution of 1.2 g of 4-hydroxy-2,6-dimethylbenzaldehyde in 12 ml of N,N-dimethylformamide was treated while stirring with 0.32 g of 55-65% sodium hydride and heated to 40°C for 15 minutes. Thereafter, a solution of 1.6 g of iodoacetamide in 4 ml of N,N-dimethylformamide was added dropwise and the mixture was heated to 40°C for a further 4 hours while stirring. The mixture was poured into 80 ml of ice-water and the solid was filtered off and washed in succession with water and diethyl ether. The residue was dissolved in ethyl acetate and the solution was washed once with 3N aqueous sodium hydroxide solution, dried over anhydrous magnesium sulphate and evaporated. Crystallization from diethyl ether yielded 0.9 g of 2-(4-formyl-3,5-dimethylphenoxy)acetamide, m.p. 157-158°C.

3-(3-Dimethylaminopropoxy)-2,6-dimethylbenzaldehyde

A solution of 1.5 g of 3-hydroxy-2,6-dimethylbenzaldehyde in 14.4 ml of ethanol and 0.6 ml of water was treated with 2.94 g of potassium carbonate. The mixture was stirred at 60°C and treated over a period of 20 minutes with 1.58 g of 3-dimethyl-

amino-1-chloropropane hydrochloride in several portions. The mixture was heated to reflux for 18 hours and thereafter cooled to room temperature. The solids were filtered off and the solvent was evaporated. The residue was dissolved in ethyl acetate and the solution was washed in succession with water, 2N sodium hydroxide solution and water. The organic phase was dried over anhydrous magnesium sulphate and the solvent was evaporated. The residue was chromatographed on silica gel with chloroform/methanol as the eluent. Distillation yielded 1.56 g of 3-(3-dimethylaminopropoxy)-2,6-dimethylbenzaldehyde, b.p. 115°C/0.1 Torr.

(2RS,6RS)- and (2R,6S)-3-(2,6-dimethylmorpholin-4-yl-methyl)-2,4,6-trimethylbenzaldehyde

(2RS,6RS)- and (2R,6S)-3-(2,6-dimethylmorpholin-4-yl-methyl)-2,4,6-trimethylbenzaldehyde, m.p. 130°C (hexane), was prepared in analogy to the procedure described above for the synthesis of 2,4,6-trimethyl-3-morpholin-4-yl-methyl-benzaldehyde.

2,4,6-Trimethyl-3-piperidin-1-yl-methylbenzaldehyde

2,4,6-Trimethyl-3-piperidin-1-yl-methylbenzaldehyde, m.p. 70°C (hexane), was prepared in analogy to the manner described above for the synthesis of 2,4,6-trimethyl-3-morpholin-4-yl-methylbenzaldehyde.

(S)-3-(2-Hydroxymethyl-pyrrolidin-1-yl-methyl)-2,4,6-trimethylbenzaldehyde

(S)-3-(2-Hydroxymethyl-pyrrolidin-1-yl-methyl)-2,4,6-trimethylbenzaldehyde, b.p. 250°C/0.2 Torr, was prepared in analogy to the procedure described above for the synthesis of 2,4,6-trimethyl-3-morpholin-4-yl-methylbenzaldehyde.

2-(Benzyloxymethyl)benzaldehyde

(i) A solution of 66.4 g of benzyl 2-(benzyloxymethyl)benzoate in 200 ml of ethanol was treated with a solution of 16.0 g of sodium hydroxide in 50 ml of water. The mixture was heated to reflux for 16 hours while stirring and concentrated to a small volume. The residue was diluted with 400 ml of water and the solution was extracted twice with diethyl ether. The aqueous solution was acidified with concentrated hydrochloric acid and extracted twice with diethyl ether. The latter organic extracts were combined, dried over anhydrous magnesium sulphate and the solution was evaporated to dryness. Recrystallization of the residue from hexane yielded 19.8 g of 2-(benzyloxymethyl)benzoic acid, m.p. 90-92°C.

(ii) A solution of 19.8 g of 2-(benzyloxymethyl)benzoic acid in 165 ml of diethyl ether was added dropwise at room temperature while stirring to a suspension of 4.66 g of lithium aluminium hydride in 490 ml of diethyl ether. The mixture was heated to reflux for 1 hour and thereafter cooled to room temperature. Thereafter, 35 ml of water were added dropwise, the mixture was stirred at room temperature for 10 minutes and filtered. The organic solution was dried over anhydrous magnesium sulphate and evaporated to yield 18.2 g of 2-(benzyloxymethyl)benzyl alcohol as an oil.

(iii) 3.4 ml of dimethyl sulphoxide were added dropwise at -60°C over a period of 5 minutes while stirring to a solution of 2 ml of oxalyl chloride in 50 ml of dichloromethane. The mixture was stirred at -60°C for a further 10 minutes and thereafter treated at -60°C over a period of 5 minutes while stirring with a solution of 4.56 g of 2-(benzyloxymethyl)benzyl alcohol in 20 ml of dichloromethane. Thereafter, triethylamine was added dropwise and the mixture was left to warm to room temperature. The mixture was diluted with 100 ml of water, the phases were separated and the aqueous solution was extracted with 100 ml of dichloromethane. The combined organic solutions were dried over

anhydrous magnesium sulphate and concentrated to yield 4.1 g of 2-(benzyloxymethyl)benzaldehyde as an oil.

3-Chloromethyl-2,6-dimethylbenzaldehyde

(i) A suspension of 5 g of 3-chloromethyl-2,6-dimethylbenzoic acid in 5 ml of thionyl chloride was stirred at room temperature for 2.5 hours. The excess thionyl chloride was evaporated and the residue was purified by distillation. 4.6 g of 3-chloromethyl-2,6-dimethylbenzoyl chloride, b.p. 165°C/12 Torr, were obtained.

(ii) 4.5 g of 3-chloromethyl-2,6-dimethylbenzoyl chloride were added dropwise at room temperature while stirring to 70 ml of methanol. Thereafter, the mixture was stirred at room temperature for 3 hours and the excess methanol was evaporated. Purification of the residue by distillation yielded 4.1 g of methyl 3-chloromethyl-2,6-dimethylbenzoate, b.p. 90°C/0.08 Torr, which crystallized upon standing (m.p. 38-41.5°C).

(iii) 50 ml of a 1.2M solution of diisobutyl aluminium hydride in toluene were added while stirring at 0°C over a period of 10 minutes to a solution of 3.2 g of methyl 3-chloromethyl-2,6-dimethylbenzoate in 50 ml of tetrahydrofuran. The mixture was then stirred at 0°C for a further 3.5 hours, thereafter treated in succession with 5 ml of ethyl acetate and 25 ml of 2N hydrochloric acid at 0°C while stirring. The mixture was stirred at room temperature for a further hour and extracted twice with ethyl acetate. After drying over anhydrous magnesium sulphate the solvent was evaporated. Recrystallization of the residue from hexane yielded 2.3 g of 3-chloromethyl-2,6-dimethylbenzyl alcohol, m.p. 96-98°C.

(iv) A solution of 1.5 g of 3-chloromethyl-2,6-dimethylbenzyl alcohol in 50 ml of dichloromethane was treated with 6.9 g of manganese dioxide and stirred at room temperature for 18 hours. The mixture was filtered and the solvent was evaporated. The residue was chromatographed on silica gel with hexane/ethyl

acetate and yielded 0.6 g of 3-chloromethyl-2,6-dimethylbenzaldehyde, m.p. 52-56°C.

Examples A-E illustrate the production of pharmaceutical preparations.

Example A

Hard gelatine capsules can be produced as follows:

Ingredient		mg/capsule
1.	Spray-dried powder containing 75% compound I	20
2.	Sodium dioctylsulphosuccinate	0.2
3.	Sodium carboxymethylcellulose	4.8
4.	Microcrystalline cellulose	86.0
5.	Talc	8.0
6.	Magnesium stearate	1.0
	Total	120

The spray-dried powder, which is based on the active ingredient, gelatine and microcrystalline cellulose and which has an average active ingredient particle size of <1μ (measured using autocorrelation spectroscopy), is moistened with an aqueous solution of sodium carboxymethylcellulose and sodium dioctylsulphosuccinate and kneaded. The resulting mass is granulated, dried and sieved, and the granulate obtained is mixed with microcrystalline cellulose, talc and magnesium stearate. The powder is filled into size 0 capsules.

Example B

Tablets can be produced as follows:

Ingredient		mg/tablet
1.	Compound I as a finely milled powder	20
2.	Powd. lactose	100
3.	White corn starch	60
4.	Povidone K30	8
5.	White corn starch	112
6.	Talc	16
7.	Magnesium stearate	4
	Total	320

The finely milled substance is mixed with lactose and a portion of the corn starch. The mixture is moistened with an aqueous solution of Povidone K30 and kneaded, and the resulting mass is granulated, dried and sieved. The granulate is mixed with the remaining corn starch, talc and magnesium stearate and pressed to tablets of suitable size.

Example C

Soft gelatine capsules can be produced as follows:

Ingredient		mg/capule
1.	Compound I	5
2.	Triglyceride	450
	Total	455

10 g of compound I are dissolved in 90 g of medium-chain triglyceride while stirring and with inert gasification and protection from light. This solution is processed as a capsule fill mass to soft gelatine capsules containing 5 mg of active ingredient.

Example D

A cream can be produced in a manner known per se from the constituents listed hereinafter:

	Wt.%
Compound of formula I	0.1-5
Cetyl alcohol	5.25-8.75
Arlacel 165 (glyceryl/PEG 100 stearate)	3.75-6.25
Miglyol 818 (caprylic/capric/linoleic acid triglyceride)	11.25-18.75
Sorbitol solution	3.75-6.25
Na_2 EDTA	0.075-0.125
Carbopol 934P (carbomer 934P)	0.15-0.25
Butylated hydroxyanisole	0.0375-0.0625
Methylparaben	0.135-0.225
Propylparaben	0.0375-0.0625
NaOH (10% solution)	0.15-0.25
Water q.s.	100.00

Example E

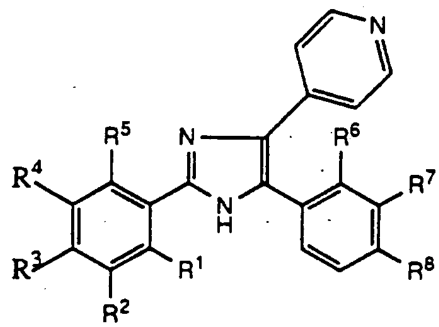
A gel can be produced in a manner known per se from the constituents listed hereinafter:

	Wt.%
Compound of formula I	0.1-5
Pluronic L 101 (poloxamer 331)	10.00
Aerosil 200 (silicon dioxide)	8.00
PCL liquid (fatty acid ester	15.00
Cetiol V (decyl oleate)	20.00
Neobee oil (medium chain length triglyceride)	15.00
Euhanol G (octyldodecanol), q.s.	100.00

The physical properties of the preparations can be altered by varying the ratio between the adjuvants in Examples D and E.

Claims

1. Imidazole derivatives of the general formula



wherein R^1-R^8 each independently signify hydrogen, lower-alkyl, substituted lower alkyl, lower-alkenyl, lower-alkoxy, substituted lower alkoxy, lower-alkoxycarbonyl, halogen, hydroxy, amino, mono- or di-(lower-alkyl)amino or nitro, and pharmaceutically usable salts thereof.

2. Imidazole derivatives in accordance with claim 1, wherein R^1 signifies lower-alkyl or halogen, R^2 signifies hydrogen, hydroxy, nitro, lower-alkoxycarbonyl, di(lower-alkyl)amino-lower-alkyl, morpholino-lower-alkyl or 4-methylpiperazinyl-lower-alkyl, R^3 signifies hydrogen or lower-alkyl, R^4 signifies hydrogen, R^5 signifies amino or lower-alkyl, R^6 signifies hydrogen, R^7 signifies hydrogen or lower-alkyl and R^8 signifies hydrogen or halogen.

3. 4-[5-(4-Chlorophenyl)-2-(2,4,6-trimethylphenyl)-imidazol-4-yl]pyridine,

4. 4-[5-(3-methylphenyl)-2-(2,4,6-trimethylphenyl)-imidazol-4-yl]pyridine,

5. 3-chloro-2-[4-(4-chlorophenyl)-5-pyridin-4-yl-imidazol-2-yl]phenylamine,

6. 4-[5-(4-chlorophenyl)-2-(2,6-diisopropylphenyl)-imidazol-4-yl]pyridine,

7. methyl 3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzoate,

8. 4-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]morpholine,

9. [3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]dimethylamine,

10. 1-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]-4-methylpiperazine,

11. 4-[5-(4-chlorophenyl)-2-(2,4,6-trimethyl-3-nitrophenyl)imidazol-4-yl]pyridine and

12. 3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylphenol.

13. 4-[5-(3-Chlorophenyl)-2-(2,4,6-trimethylphenyl)-imidazol-4-yl]pyridine,

4-[5-(3,4-dichlorophenyl)-2-(2,4,6-trimethylphenyl)-imidazol-4-yl]pyridine,

4-[5-(4-fluorophenyl)-2-(2,4,6-trimethylphenyl)imidazol-4-yl]pyridine,

4-[5-(4-chlorophenyl)-2-(2,6-dichlorophenyl)imidazol-4-yl]pyridine,

4-[5-(2,4-dichlorophenyl)-2-(2,6-dichlorophenyl)imidazol-4-yl]pyridine,

4-[5-(4-chlorophenyl)-2-(2,6-dimethylphenyl)imidazol-4-yl]pyridine,

4-[5-(4-chlorophenyl)-2-(2,3,4,5,6-pentamethylphenyl)-imidazol-4-yl]pyridine,

4-[5-(2-fluorophenyl)-2-(2,4,6-trimethylphenyl)imidazol-4-yl]pyridine,

4-[5-(3-methoxyphenyl)-2-(2,4,6-trimethylphenyl)-

imidazol-4-yl]pyridine,
4-[5-(3-bromophenyl)-2-(2,4,6-trimethylphenyl)imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(2,6-dibromophenyl)imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(2-chloro-6-methylphenyl)-imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(2-chloro-6-nitrophenyl)imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(2-methyl-6-nitrophenyl)-imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(2-chloro-6-fluorophenyl)-imidazol-4-yl]pyridine,
4-[5-(3-chlorophenyl)-2-(2-chloro-6-nitrophenyl)imidazol-4-yl]pyridine,
4-[5-(3,4-dichlorophenyl)-2-(2-chloro-6-nitrophenyl)-imidazol-4-yl]pyridine,
4-[5-(4-fluorophenyl)-2-(2-chloro-6-nitrophenyl)imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(2-bromo-6-methylphenyl)-imidazol-4-yl]pyridine,
4-[5-(4-bromophenyl)-2-(2-chloro-6-nitrophenyl)imidazol-4-yl]pyridine,
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4-[5-(3-bromophenyl)-2-(2-chloro-6-nitrophenyl)imidazol-4-yl]pyridine,
4-[5-(3-methoxyphenyl)-2-(2-chloro-6-nitrophenyl)-imidazol-4-yl]pyridine,
4-[5-(4-fluorophenyl)-2-(2-bromo-6-methylphenyl)-imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(2-bromo-3-methylphenyl)-imidazol-4-yl]pyridine,
4-[5-(4-fluorophenyl)-2-(2-methyl-6-nitrophenyl)-imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(2-bromophenyl)imidazol-4-

yl]pyridine,
4-[5-(3-bromophenyl)-2-(2-bromophenyl)imidazol-4-yl]pyridine,
dimethyl-[2-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-3-methylphenyl]amine,
4-[2-(3-bromo-2,6-dimethylphenyl)-5-(4-chlorophenyl)-imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(2,6-dimethyl-3-nitrophenyl)-imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(2-fluoro-6-trifluoromethyl-phenyl)imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(2-allyl-6-methylphenyl)-imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(2-methoxymethyl-6-methyl-phenyl)imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(3-methoxy-2,6-dimethylphenyl)-imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(2,6-dimethyl-3,5-dinitrophenyl)-imidazol-4-yl]pyridine,
4-[5-(4-chlorophenyl)-2-(2-chloro-6-trifluoromethyl-phenyl)imidazol-4-yl]pyridine,
1-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]-4-methylpiperazine,
3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4-dimethylphenol,
4-[4-(4-chlorophenyl)-5-pyridin-4-yl-imidazol-2-yl]-3,5-dimethylphenol,
ethyl 1-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]piperidin-4-carboxylate,
ethyl [4-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-3,5-dimethylphenoxy]acetate,
4-[2-(3-azidomethyl-2,4,6-trimethylphenyl)-5-(4-chloro-phenyl)imidazol-4-yl]pyridine,
[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylphenyl]acetonitrile,
3-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4-dimethylphenoxy]propan-1-ol,
[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-

benzyl]diethylamine,

4-[5-(4-chlorophenyl)-2-(2,3,6-trichlorophenyl)imidazol-4-yl]pyridine,

4-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-3,5-dimethylphenoxy]acetamide,

[3-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4-dimethylphenoxy]propyl]dimethylamine,

(2RS,6RS)- and (2R,6S)-4-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]-2,6-dimethylmoropholine,

4-[5-(4-chlorophenyl)-2-(2,4,6-trimethyl-3-piperidin-1-yl-methylphenyl)-imidazol-4-yl]pyridine,

(S)-[1-[3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl]pyrrolidin-2-yl]methanol,

3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4-dimethylbenzyl acetate,

3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylbenzyl acetate,

3-[4-pyridin-4-yl-2-(2,4,6-trimethylphenyl)imidazol-5-ylphenol,

2-[4-pyridin-4-yl-2-(2,4,6-trimethylphenyl)imidazol-5-yl]phenylmethanol,

3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4-dimethylphenylamine,

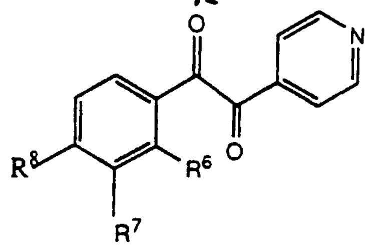
3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4,6-trimethylphenyl)methanol,

3-[5-(4-chlorophenyl)-4-pyridin-4-yl-imidazol-2-yl]-2,4-dimethyl-phenylmethanol,

3-[5-(4-chlorophenyl)-4-pyridin-4-yl)imidazol-2-yl]-2,4,6-trimethylphenylamine.

14. Pharmaceutical preparations containing a compound of any one of claims 1-13 and usual pharmaceutical carriers.

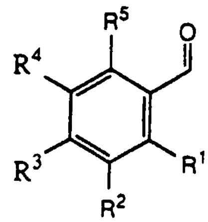
15. A process for the manufacture of compounds set forth in claim 1, which process comprises reacting a diketone of the general formula



(II)

wherein R^6, R^7 and R^8 have the significance given in claim 1,

with an aldehyde of the general formula



(III)

wherein R^1, R^2, R^3, R^4 and R^5 have the significance given in claim 1 and wherein a hydroxy group in the compounds of formulae II and III can be present in protected form,

in the presence of ammonia, cleaving off a hydroxy protecting group which may be present and, if desired, functionally modifying reactive groups present in a compound of formula I obtained and, if desired, converting a compound of formula I into a pharmaceutically usable salt.

16. Compounds set forth in claim 1, insofar as they are manufactured according to the process claimed in claim 15 or an obvious chemical equivalent thereof.

17. The use of the compounds set forth in claim 1 as medicaments.

18. The use of the compounds set forth in claim 1 for the production of pharmaceutical preparations for the therapy and prophylaxis of athersclerosis, psoriasis, tumours or alopecia.

19. The invention as hereinbefore described.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/04741

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/04 A61K31/415 C07D233/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE,A,22 21 546 (CIBA-GEIGY AG) 16 November 1972 see claims 31-59 ---	1-18
X	US,A,3 772 441 (LOMBARDINO J) 13 November 1973 see the whole document ---	1-18
X	WO,A,93 14081 (SMITHKLINE BEECHAM CORP) 22 July 1993 see the whole document ---	1-18
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
10 April 1996	-3. 05. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stellmach, J

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PROC.NATL.ACAD.SCI.USA, vol. 87, January 1990 WASHINGTON, pages 782-785, POLI,G. ET AL. 'Tumor necrosis factor alpha functions in an aurocrine manner in the induction of human immunodeficiency virus expression ' see the whole document ---	1-18
Y	INT.J.BIOCHEM., vol. 26, no. 10/11, 1994 OXFORD, pages 1203-1226, BOUTIN,J.A. 'Tyrosin Protein Kinase Inhibition and Cancer ' see the whole document ---	1-18
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